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Author(s): LaVecchia L (REPRINT) ; Ometto R; Finocchi G; Vincenzi M
Corporate Source: OSPED CIVILE S BORTOLO,DIV CARDIOL, VIALE RODOLFI/I-36100
   VICENZA//ITALY/ (REPRINT); ULSS 6,DIV CLINICIZZATA
   CARDIOL/VICENZA//ITALY/
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ISSN: 0147-8389

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   Publishing Model Print
   Document type: Journal Article; Review; Review, Tutorial
   Languages: ENGLISH

3) Clinical profiles of four large pedigrees with familial dilated
   cardiomyopathy : preliminary recommendations for clinical practice.
   Crispell K A; Wray A; Ni H; Nauman D J; Hershberger R E
   Department of Medicine, Oregon Health Sciences University, Portland
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272-0830

Cardiomyopathy

Clinical Profiles of Four Large Pedigrees With Familial Dilated Cardiomyopathy

Preliminary Recommendations for Clinical Practice

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OBJECTIVES	This study aimed to characterize the clinical profile of familial dilated cardiomyopathy (FDC) in the families of four index patients initially diagnosed with idiopathic dilated cardiomyopathy (IDC) and to provide clinical practice recommendations for physicians dealing with these diseases.
BACKGROUND	Recent evidence indicates that approximately one-half of patients diagnosed with IDC will have FDC, a genetically transmissible disease, but the clinical profile of families screened for FDC in the U.S. has not been well documented. Additionally, recent ethical guidelines suggest increased responsibilities in caring for patients with newly found genetic cardiovascular disease.
METHODS	After identification of four families with FDC, we undertook clinical screening including medical history, physical examination, electocardiogram and echocardiogram. Diagnostic criteria for FDC-affected status of asymptomatic family members was based on left ventricular enlargement (LVE). Subjects with confounding cardiovascular diagnoses or body mass indices >35 were excluded.
RESULTS	We identified 798 living members from the four FDC pedigrees, and screened 216 adults and 129 children (age <16 years). Twenty percent of family members were found to be affected with FDC; 82.8% of those affected were asymptomatic. All four pedigrees demonstrated autosomal dominant patterns of inheritance. The average left ventricular end-diastolic dimension was 61.4 mm for affected and 48.4 mm for unaffected subjects, with an average age of 38.3 years ($\pm$14.6 years) for affected and 32.1 years for unaffected subjects. The age of onset for FDC varied considerably between and within families. Presenting symptoms when present were decompensated heart failure or sudden death.
CONCLUSIONS	We propose that with a new diagnosis of IDC, a thorough family history for FDC should be obtained, followed by echocardiographic-based screening of first-degree relatives for LVE, assuming their voluntary participation. If a diagnosis of FDC is established, we suggest further screening of first-degree relatives, and all subjects with FDC undergo medical treatment following established guidelines. Counseling of family members should emphasize the heritable nature of the disease, the age-dependent penetrance and the unpredictable clinical course. (J Am Coll Cardiol 1999;34:837–47) © 1999 by the American College of Cardiology

Heart failure is a major cause of death and disability in several million U.S. citizens resulting principally from ischemic and idiopathic dilated (IDC) cardiomyopathies. Ischemic cardiomyopathy results from loss of myocardium from one or more myocardial infarctions. In contrast, the causes of IDC have been postulated to result from a variety of viral,

toxic or environmental injuries (1) and, more recently, familial transmission. Early in this decade, it was suggested that up to 20% of patients initially diagnosed with IDC would have familial disease (2,3). More recent results (4,5) suggest that from 35% to 48% of patients with IDC may have familial disease. This familial disease most commonly follows a Mendelian dominant inheritance pattern (4–6), and thus has been postulated to represent genetic disease. In support of this genetic hypothesis are reports of six pedigrees with autosomal dominant transmission and positive linkage to five chromosomes (6–11) or to actin in two very small pedigrees (12). These data suggest that familial dilated cardiomyopathy (FDC) involves several different genes or gene families.

Abbreviations and Acronyms	
ACE	= angiotensin-converting enzyme
BMI	= body mass index
ECG	= electrocardiogram
FDC	= familial dilated cardiomyopathy
HCM	= hypertrophic cardiomyopathy
ICD	= internal cardiac defibrillator
IDC	= idiopathic dilated cardiomyopathy
LVE	= left ventricular enlargement
LVEDD	= left ventricular end-diastolic dimension
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
OHSU	= Oregon Health Sciences University
SOLVD	= Studies of Left Ventricular Dysfunction

Thus, we now understand that a patient newly diagnosed with IDC has a one in three or greater chance of having a serious, potentially life-threatening heritable myocardial disease. This new insight of genetic cardiomyopathy necessitates scrutiny of our current practice patterns. Are our current diagnostic and therapeutic approaches adequate for patients newly diagnosed with IDC? If IDC represents a heritable disease, what obligations do we have to the potentially affected family members? In 1993, we established a research program to identify and characterize families with FDC and to determine the molecular basis of FDC. We have screened numerous patients who by family history may have FDC, and have undertaken clinical screening of four large families. In this paper, we present the clinical characteristics of these families, and we base our clinical practice recommendations on these observations.

METHODS

Oregon Health Sciences University (OHSU) program description and FDC screening questionnaire. An FDC research program was established at the OHSU in 1993 to determine the molecular basis of FDC. All new patients who were referred to the clinic of the Oregon Heart Failure Treatment Program at OHSU after informed consent were asked to complete an FDC screening questionnaire containing questions regarding their diagnosis, duration, symptoms and etiology of heart failure, including detailed information on family history. A patient was diagnosed as having FDC if IDC was present in one first-degree relative or two second-degree relatives. We selected four index patients with large families consisting of three or more living generations for prospective and comprehensive clinical screening for FDC.

Clinical screening of families. Informed consent was obtained from all subjects. Adult relatives of each index patient were contacted either by phone or by mail to obtain personal medical histories and demographic information. Pedigree construction for each family was undertaken. Medical records and/or death certificates were retrieved. Each family

member was offered clinical screening consisting of a medical history, a physical examination, a 12-lead electrocardiogram (ECG) and a two-dimensional and M-mode ECG. diogram. Local and distant clinical screenings were conducted between 1993 and 1998 for OHSU FDC-1, 2, 3 and 4. Initial clinical screening has been completed for FDC-1; clinical screening for FDC-2, 3 and 4 is still in progress.

History and physical examination. The medical history documented cardiovascular disease including hypertension, heart disease, arrhythmia, stroke or transient ischemic attacks, diabetes mellitus, lung and thyroid disease. Review of systems included questions about dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, energy level, appetite, weight change, edema, activity level, chest pain, palpitations and syncope or presyncopal symptoms. Additionally, we obtained a pregnancy history and a history for alcohol, tobacco, medication and illicit drug use from each family member. The physical examination included vital signs, weight and height measurements, as well as assessment for elevated jugular venous pressure, carotid artery quality, bruits, lifts, heaves, quality and location of the point of maximal impulse, presence of a third or fourth heart sound, murmurs, quality of breath sounds, hepatic size and presence of peripheral edema.

Echocardiographic methods. Echocardiograms were performed by experienced operators without knowledge of the family member's clinical data, using high-quality echocardiographic equipment. Two-dimensional and M-mode parasternal long- and short-axis views were obtained in addition to apical four- and two-chamber views. Examinations were recorded on VHS videocassette tapes and strip charts when possible, using 2.5- and 3.5-MHz transducers. The echocardiograms were independently reviewed by two experienced physicians to verify the accuracy of measurements and to interpret the studies. Measurements were taken from the parasternal long- or short-axis M-mode or two-dimensional views. Left ventricular dimensions were measured according to the American Society of Echocardiography.

We defined left ventricular enlargement (LVE) in subjects 16 years of age or older as a left ventricular end-diastolic dimension (LVEDD) > Framingham 97.5 percentile standard (13). This method is gender and height specific, and its use is based on the recommendation by Vasan et al., who analyzed echocardiographic data from the Framingham Heart Disease Study (14). The 97.5 percentile values of LVEDD are calculated as:

Males: $LVEDD97.5 = \exp(3.5990 + 0.5721 \times \ln Height + 1.96 \times 0.0835)$

Females: $LVEDD97.5 = \exp(3.5856 + 0.4963 \times \ln Height + 1.96 \times 0.0635)$

Table 1. Characteristics of Four Large OHSU FDC Pedigrees

	FDC-1	FDC-2	FDC-3	FDC-4	Total
Total living	158	104	481	55	798
Total screened	107	59	152	27	345
Children (<16 yrs) (%)	46 (43.0)	17 (28.8)	56 (36.8)	10 (37.0)	129 (37.4)
Adults (%)	61 (57.0)	42 (71.2)	96 (63.2)	17 (63.0)	216 (62.6)
Age at screening (yrs)	23	20	24	18.8	21.4
Median (range)	(1–65)	(5–75)	(0.67–75)	(1.8–47.0)	(0.7–75.0)
Gender					
Male (%)	50 (46.7)	32 (54.2)	72 (47.4)	15 (55.6)	169 (49.0)
Female (%)	57 (53.2)	27 (45.8)	80 (52.6)	12 (44.4)	176 (51.0)
Smoker	35 (32.7)	10 (16.9)	44 (28.9)	9 (33.3)	98 (28.4)
Former (%)	8 (7.5)	3 (5.1)	13 (8.5)	6 (22.2)	30 (8.7)
Current (%)	27 (25.2)	7 (11.9)	31 (20.4)	3 (11.1)	68 (19.7)
Medical history					
Hypertension	3 (2.8)	6 (10.2)	21 (13.8)	1 (3.7)	31 (9.0)
Diabetes	3 (2.8)	2 (3.4)	5 (3.3)	0	10 (2.9)
Arrhythmias	4 (3.7)	7 (11.9)	6 (3.9)	1 (3.7)	18 (5.2)
Coronary artery disease	1 (0.9)	1 (1.7)	1 (0.7)	0	3 (0.9)
BSA (m^2)	1.75	1.85	1.80	1.87	1.84
Median (range)	(0.47–2.54)	(0.83–2.61)	(0.24–2.92)	(0.54–2.41)	(0.25–2.9)
BMI (kg/m^2)	25.1	24.9	26.0	24.5	25.6
Median (range)	(12.6–52.9)	(14.5–47.4)	(13.8–110.9)	(15.5–34.5)	(12.6–110.9)

BMI = body mass index; BSA = body surface area; FDC = familial dilated cardiomyopathy; OHSU = Oregon Health Sciences University.

Assignment of affected, nonaffected and indeterminate status. All assignments were based on the phenotype observed at screening, or on medical records to establish the diagnosis of IDC. Subjects of all ages were classified as affected if they had an established diagnosis of IDC, or they were 16 years of age or older with LVE (13) and no other confounding issues. Patients of all ages with normal LV size were classified as nonaffected regardless of other confounding issues. Indeterminate status was assigned to two categories of subjects: 1) those without echo data (nonevaluable, usually from no echo window), and 2) those with LVE, but also with some other confounding cardiovascular diagnosis or other cardiovascular abnormality detected in the screening protocol or age <16 years of age. Cardiovascular diagnoses included a history of severe and/or uncontrolled hypertension (defined as repeated systolic blood pressures > 160 mm Hg and/or diastolic blood pressures > 100 mm Hg), a history of hypertension that was treated with medications, any history of ischemic heart disease, congenital heart disease, intrinsic valvular disease, history of cardiotoxic chemotherapy or radiation therapy involving the chest, or with moderately severe obesity defined as a body mass index (BMI) greater than 35 kg/m^2. These criteria for the assignment of affected, nonaffected and indeterminate status are referred to as the OHSU FDC diagnostic criteria (13).
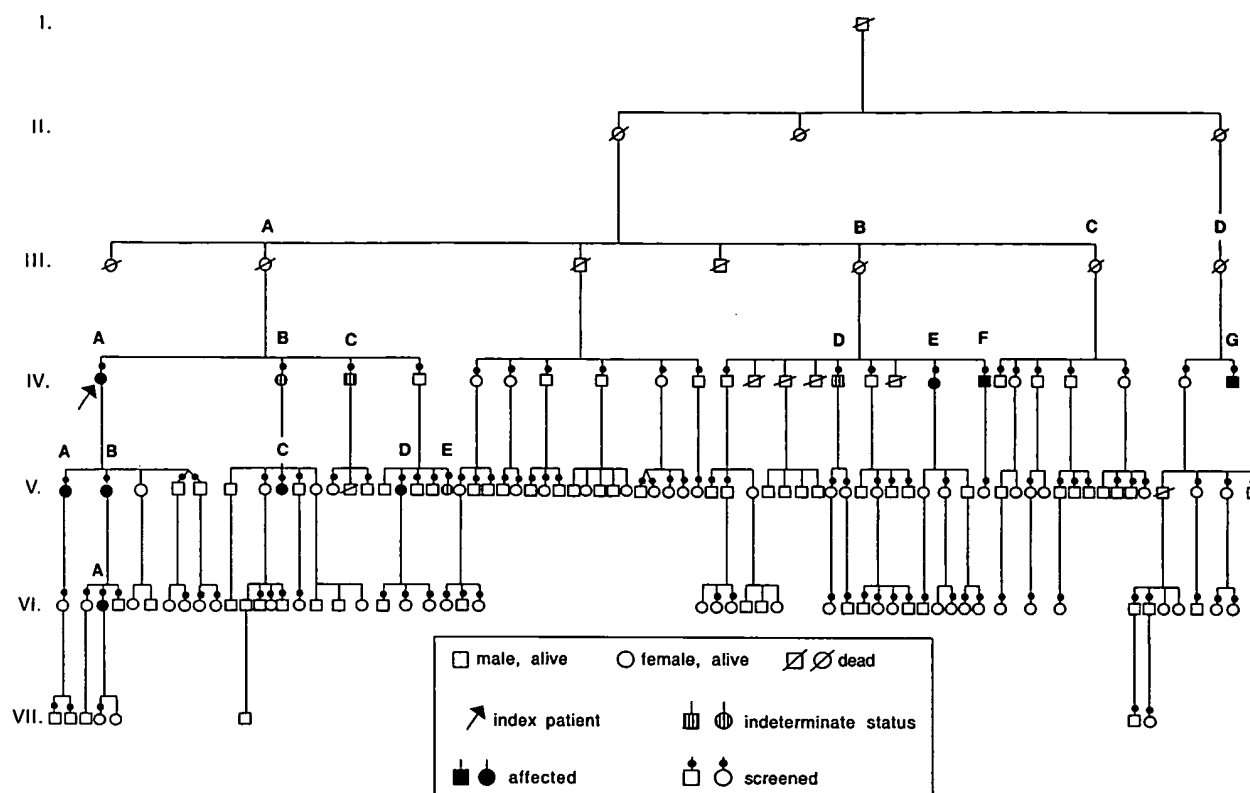
Statistical analysis. When comparing the characteristics of family members with and without the FDC phenotype, we subsequently excluded the family members who had a history of hypertension or coronary artery disease, an inadequate echocardiogram or BMI >35 kg/m^2. The Student *t* test and chi-square test or Fisher exact test were used for the comparison. Statistical significance indicates $p < 0.05$ unless otherwise noted. The statistical analysis was performed using statistical software SPSS-PC (SPSS Inc., Chicago, Illinois).

RESULTS

Pedigree descriptions and clinical profiles. We identified a total of 798 living members from the four FDC pedigrees. Clinical screening has been completed in 345 family members, and their clinical characteristics are given (Table 1). Approximately 40% of family members from each pedigree were children (age <16-years-old). The median age of screened family members was 21.4 years (range 8 months to 75 years). The age distribution was similar in the four pedigrees. Approximately 1 out of 10 relatives had a history of hypertension. The average body surface area and BMI are comparable across the four pedigrees.

OHSU FDC-1. The index patient of OHSU FDC-1 (Fig. 1) was 63 years old at the time of identification. She was a New York Heart Association (NYHA) functional class 2 when diagnosed with IDC at 49 years of age. Her symptoms have progressed and she is currently a NYHA functional class 3. Her LVEDD is 70 mm with a fractional shortening of 14%; her left ventricular ejection fraction (LVEF) is 0.35. Her ECG shows a left bundle branch block. She has been treated with conventional medications including angiotensin-converting enzyme (ACE) inhibitors, digoxin, diuretics and beta blockers. Her oldest daughter (V-A) and

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Figure 1. Pedigree of OSHU FDC-1. OHSU FDC-1 is a white family comprised of 165 relatives. It has seven generations (circa 1850 to 1995). The family has a wide geographic distribution ranging from Alaska and the western U.S. to the Midwest and southern U.S.

a distant cousin (IV-G) had symptomatic IDC confirmed by medical records and formed the basis for diagnosis of FDC; both were treated with ACE inhibitors, and left ventricular size and function have improved.

OHSU FDC-1 had a low prevalence of hypertension, diabetes and coronary artery disease (Table 1). All members of the first three generations were deceased; medical histories suggest that four of the seven members of generation III may have had heart failure (III-A, III-B, III-C, III-D), and these subjects died in their fifth and sixth decades of life. One hundred seven of 158 living family members ranging from 1 to 65 years of age were screened (Table 1). Six family members (IV-E, IV-F, V-B, V-C, V-D, VI-A) were identified by prospective screening as affected. All were asymptomatic with normal cardiovascular physical examinations. Subjects IV-B and IV-C were classified as indeterminate because of poor-quality echocardiograms. Subjects IV-D and V-E were classified as indeterminate because of BMI >35 kg/m² and exposure to cardiotoxic chemotherapy, respectively.

Pedigree analysis suggests an autosomal dominant pattern of inheritance (Fig. 1). This family expresses a mild form of FDC with the onset of symptoms occurring in mid to later in life. The index patient and symptomatic family members have responded favorably to medical therapy.

OHSU FDC-2. One of the unique aspects of the OHSU FDC-2 pedigree is that the index patient has both a maternal and paternal family history of dilated cardiomyopathy (Fig. 2). The index patient for OHSU FDC-2 was 14 years old when he was identified. He was asymptomatic until May 1993, when he became acutely short of breath and was hospitalized with a diagnosis of heart failure; his LVEDD was 71 mm with a fractional shortening of 11%; his LVEF was 0.15. His ECG showed a Q-wave pattern in V1-V4. He was diagnosed with IDC and underwent emergent heart transplantation in June 1993. Routine histopathologic examination was unrevealing and consistent with IDC. This family came to our attention when a previously healthy 17-year-old maternal cousin (V-C) was resuscitated from ventricular fibrillation in November 1994. He was found to have an LVEDD of 52 mm and severely reduced left ventricular systolic function. Coronary angiography revealed normal coronary arteries. Conventional medical therapy with ACE inhibitors was initiated. He later had an internal cardiac defibrillator (ICD) placed. His ventricular function has improved. This event prompted careful medical and family histories for both parents of the index patient. Remarkably, at prospective screening, both parents were found to have IDC, and on that basis a diagnosis of
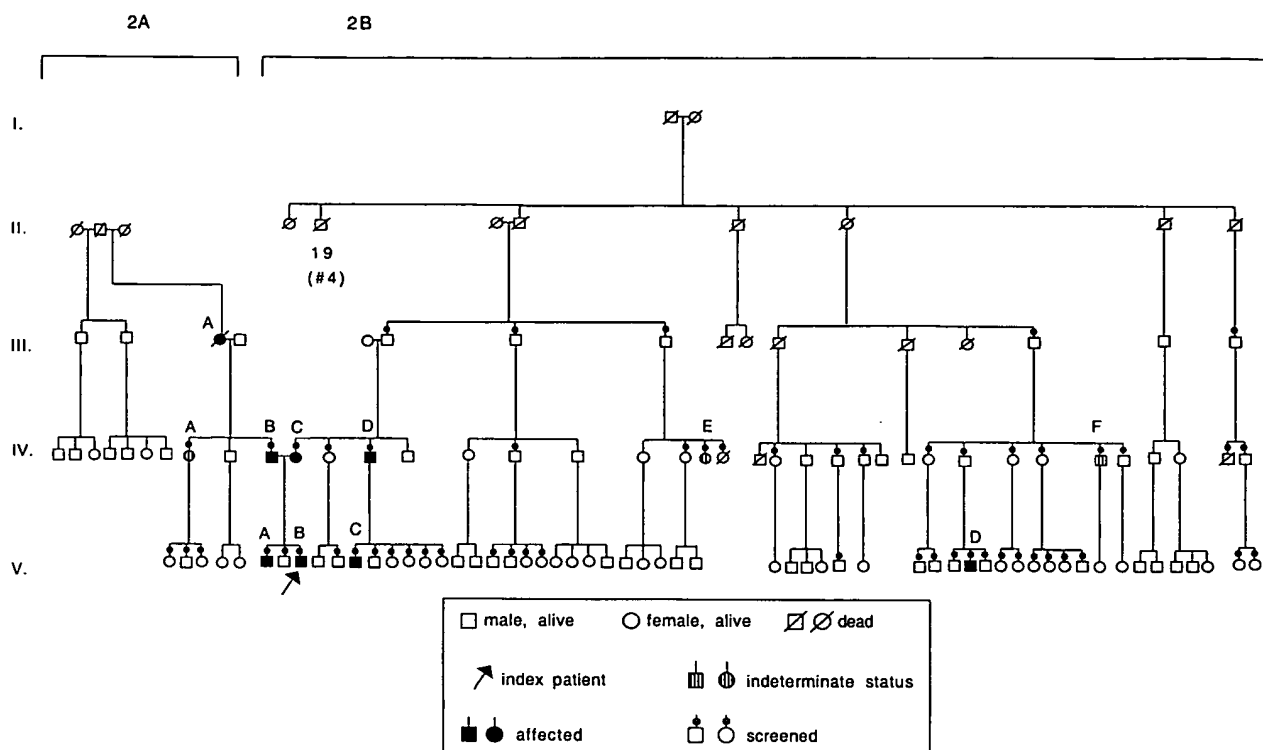
Figure 2. Pedigree of OHSU FDC-2. OHSU FDC-2 is comprised of two Caucasian families spanning five generations that includes 20 paternal (A) and 84 maternal (B) relatives. The index patient's paternal grandmother (III-A) died from dilated cardiomyopathy at the age of 51 years. The geographic distribution of these families range from the Pacific Northwest to the Midwest and southern U.S. The number 19 below the subject symbol and the number in parentheses (#4) denote the number of known descendants and the number of screened subjects, respectively, not shown due to space limitations.

FDC was assigned. Complete family screening of both maternal and paternal pedigrees was then undertaken.

A total of 59 relatives from 5 to 75 years of age have been screened (Table 1). Five additional family members (IV-B, IV-C, IV-D, V-A, V-D) were identified by prospective screening as affected, and all were asymptomatic except IV-B (the index patient's father), who was found to be in previously undetected decompensated heart failure. Coronary angiography revealed normal coronary arteries, and he was started on digitalis, diuretics and ACE inhibitors. Three months after subject IV-D was identified as being affected by prospective screening, he experienced sudden cardiac death, was successfully resuscitated and received an ICD. Three subjects were classified as indeterminate: subject IV-A had a BMI > 35 kg/m², subject IV-E was an elite athlete and subject IV-F had a poor-quality echocardiogram.

Pedigree analysis of FDC-2 suggests an autosomal dominant pattern of inheritance (Fig. 2). The clinical profile of this two-family pedigree is complex. Onset of disease in the FDC-2B (maternal pedigree) ranges from the second to fourth decade of life. Initial symptoms of disease in FDC-2B are lethal arrhythmias. Affected subjects in FDC-2A present with symptoms of decompensated heart failure and congestion. Notably, the index patient and his

two siblings may carry either the maternal or the paternal FDC gene, or both, even though only one sibling had LVE at the time of screening.

OHSU FDC-3. The OHSU FDC-3 index patient (Fig. 3) was a 43-year-old woman who was referred to our clinic for consideration of cardiac transplantation in September 1995. She had been diagnosed with IDC after 7 months of increasing dyspnea on exertion and fatigue. Her LVEDD was 71 mm with a fractional shortening of 14%; her LVEF was 0.21 and her ECG showed ventricular bigeminy. Despite full medical therapy and stable NYHA class III symptoms, she died of sudden cardiac death in October 1996. The FDC diagnosis was established as family history revealed that her mother (III-B) and her maternal grandfather (II-A) died of heart failure at 59 and 52 years of age, respectively, and that three deceased siblings (IV-E, IV-F, IV-H) had IDC confirmed by medical records and/or death certificates (Fig. 3).

A total of 152 relatives ranging from eight months to 75 years of age have been screened (Table 1). Of five adult family members identified by prospective screening as affected, four were asymptomatic (III-E, IV-M, V-C, V-E); subject IV-G was symptomatic at the time of screening with
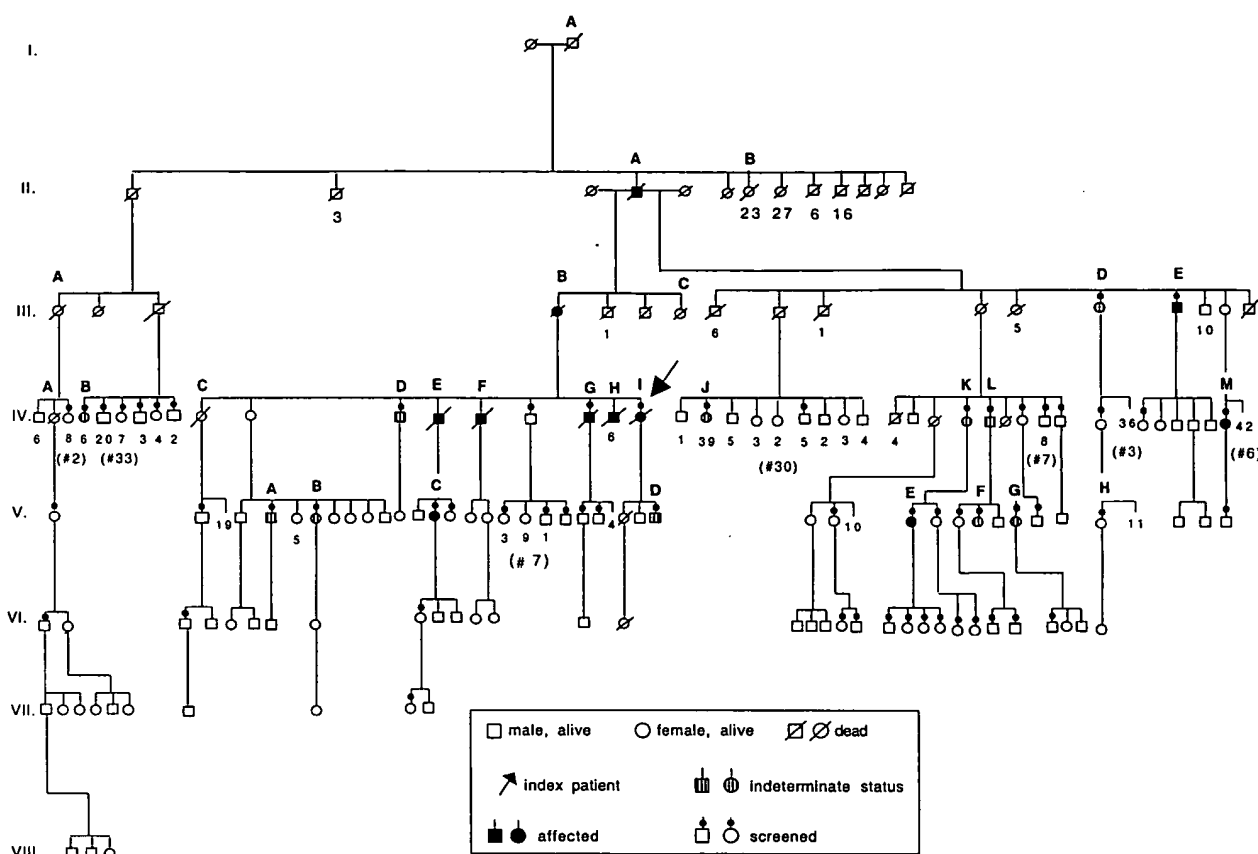
Figure 3. Pedigree of OHSU FDC-3. FDC-3 is a very large African-American family spanning eight generations with 481 living relatives who are related to the index patient by her maternal grandfather. All members of generations I and II are deceased and only four members of generation III are living. FDC-3 has a broad geographic distribution with most of the family residing in the midwestern and southern U.S., and a small portion reside in the Pacific Northwest. Numbers below the subject symbols and numbers in parentheses, i.e. **(#10)**, denote the number of known descendants and the number of screened subjects, respectively, not shown due to space limitations.

an LVEDD of 70 mm. Despite being treated with ACE inhibitors and other conventional medications, he died suddenly. At the time of screening, subject IV-K was found to have LVE, moderately reduced left ventricular function and mild symptoms of heart failure, but she was classified as indeterminate because of uncontrolled hypertension. IV-D was indeterminate because of poor-quality echo data. Eight other subjects were classified as indeterminate because of hypertension and/or obesity. FDC-3 has the highest prevalence of hypertension and obesity among the four pedigrees (Table 1). Pedigree analysis suggests an autosomal dominant pattern (Figure 3).

This African-American family is the first reported with FDC. The onset of symptoms occurs in the fifth and sixth decades of life and is expressed as congestive heart failure and/or sudden cardiac death. The disease progresses despite conventional medical therapy.

OHSU FDC-4. The OHSU FDC-4 index patient was 23 years old when diagnosed with IDC and progressive heart failure (Fig. 4). He was referred to us for consideration of

cardiac transplantation in March 1997. His LVEDD was 75 mm; his LVEF was 0.19. His ECG showed a left bundle branch block with Q-waves in V1-V3. Despite intensive medical treatment, he experienced rapid progression of heart failure and underwent cardiac transplantation in August 1997. Familial dilated cardiomyopathy was diagnosed by family history, which revealed that his paternal grandfather (II-A) died from heart failure in his 40s, and just before his transplant, a 35-year-old paternal aunt (III-K) was confirmed to have IDC and was also listed for heart transplant at another medical center. More recently, a 44-year-old paternal uncle (III-C) died from newly diagnosed IDC. Medical records have confirmed IDC and the absence of coronary artery disease in the deceased subjects II-A and II-B.

Characteristics of this family are presented (Table 1). This family has a low incidence of hypertension and no one was identified with diabetes or coronary artery disease. To date, 27 family members have been screened. An additional eight asymptomatic family members (III-B, III-D, III-F,
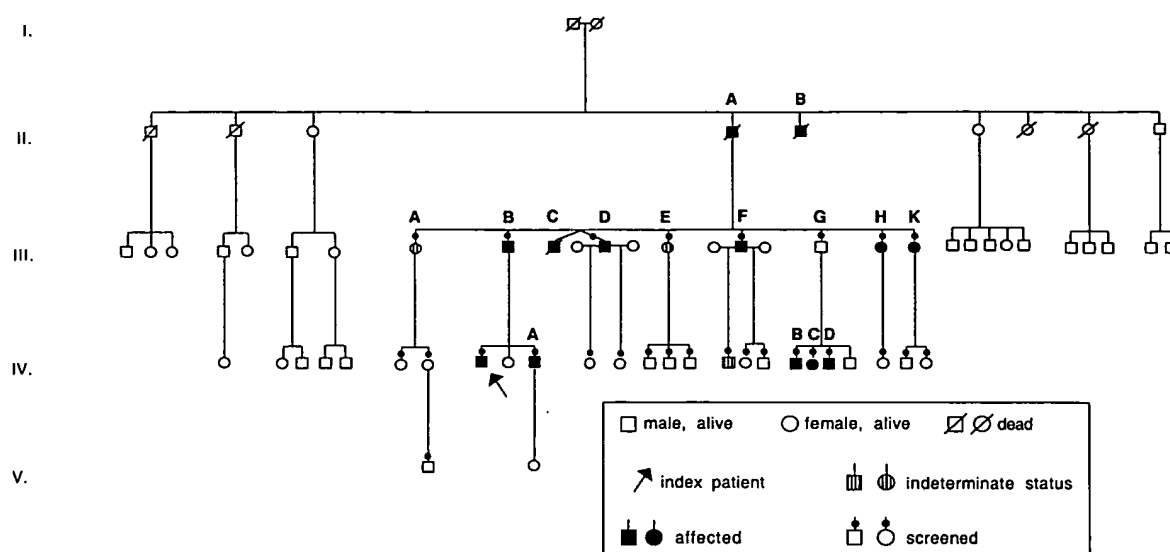
Figure 4. Pedigree of OHSU FDC-4. OHSU FDC-4 is a white pedigree that is comprised of 55 relatives from four living generations. Family members are located in the Pacific Northwest, the Southwest and the East Coast.

III-H, IV-A, IV-B, IV-C, IV-D) were identified by prospective screening as affected with FDC. Subjects III-A and III-E were classified as indeterminate because of a poor-quality echo and hypertension, respectively. One striking feature of this pedigree is the high level of penetrance (9 of 14 evaluable subjects, 64.3%). Pedigree analysis reveals an autosomal dominant pattern of inheritance. Subject III-G is an obligate carrier based on the pedigree, but has not manifested LVE at this time. Clinical screening continues for this family.

Data summary from all pedigrees. Of the 29 family members identified as affected with FDC, 24 were asymptomatic (82.8%), and are compared with nonaffected subjects from the four pedigrees (Table 2). A significant difference was observed in fractional shortening and the percentage of ECG abnormalities between affected and nonaffected subjects. The ECG abnormalities were nonspecific between pedigrees and consisted primarily of bundle branch block.

The disease phenotype, LVE, occurred as early as the second decade (Fig. 5). Although LVE increased in all four families after 35 years of age, the frequency of LVE differed considerably from family to family (Fig. 5). The variable and age-dependent penetrance of FDC has been previously noted with greater than 80% penetrance by 50 years of age (15). Thus, the data demonstrate a variation in the onset and frequency of LVE among families with FDC, and the descriptive data reflect wide variability in the onset of symptomatic heart failure or sudden cardiac death.

DISCUSSION

We have presented the clinical profiles and characteristics of four large pedigrees with FDC identified in our program

from index patients initially diagnosed with IDC. These pedigrees demonstrate autosomal dominant patterns of inheritance, the most common transmission of FDC (4–6). We also noted that most of the family members who underwent prospective clinical screening and were classified as affected by echocardiographically determined LVE were free of any signs or symptoms of cardiovascular disease. Consistent with previous studies (15), the age of onset of symptomatic clinical disease varied considerably between families and between individuals within the same family, and presenting symptoms were usually decompensated heart failure or sudden death. We suggest that these observations lay the foundation to change the clinical practice of physicians who care for patients diagnosed with IDC and FDC.

The conventional diagnosis of IDC rests upon cardiac enlargement associated with decreased systolic function (i.e., an ejection fraction less than 0.50) after other causes of cardiomyopathy have been excluded, including most commonly ischemic, valvular, inflammatory or infiltrative cardiomyopathies. If a diagnosis of clinical heart failure is appropriate, conventional medical therapy based upon ACE inhibitors, beta blockers and diuretics is indicated, as is education addressing diet, activity, medication usage and prognosis (16).

Because recent work has suggested that familial disease may account for at least 35% to 48% (4,5) of patients diagnosed with IDC, we propose that for patients with newly diagnosed IDC, additional consideration should be given to the elucidation of familial disease. Other genetically based and transmissible cardiovascular diseases have been described such as hypertrophic cardiomyopathy (HCM), which has an estimated incidence of 2.5/100,000 person-years and a prevalence of 19.7/100,000 (17). As recently

Table 2. Clinical Characteristics of Adult Family Members (>16 Years) With and Without Phenotype of Familial Dilated Cardiomyopathy

Characteristic	With Phenotype (n = 29)	Without Phenotype (n = 114*)	p Value
FDC family			
FDC-1	9 (31.0)	41 (36.0)	
FDC-2	5 (17.2)	19 (16.7)	
FDC-3	6 (20.7)	49 (43.0)	
FDC-4	9 (31.0)	5 (4.4)	
Gender			0.50
Male (%)	14 (48.3)	63 (55.3)	
Female (%)	15 (51.7)	51 (44.7)	
Age at screening (yrs)	38.3 ± 14.6†	32.1 ± 12.5	0.02
Physical exam			
Height (cm)	171.6 ± 9.3	172.3 ± 9.8	0.73
Weight (kg)	89.2 ± 22.7	84.2 ± 25.0	0.24
Heart rate (beats/min)	74.0 ± 17.1	72.0 ± 10.8	0.43
Body surface area (kg/m²)	1.9 ± 0.2	1.9 ± 0.2	0.64
Body mass index (kg/m²)	27.2 ± 3.8	26.1 ± 4.3	0.20
Blood pressure (mm Hg)			
Systolic	122.9 ± 15.7	119.1 ± 13.4	0.20
Diastolic	76.8 ± 11.1	73.2 ± 11.7	0.14
ECG (%)			< 0.01
Abnormal	11 (39.3)	25 (21.9)	
Borderline	1 (3.6)	0	
Echocardiographic			
LVEDD (mm)	61.4 ± 6.3	48.4 ± 5.0	< 0.01
Fractional shortening (%)	27.3 ± 9.9	36.4 ± 8.6	< 0.01

*Excludes members with hypertension (n = 25), coronary artery disease (n = 3), inadequate echocardiogram (n = 15) and body mass index ≥35 kg/m² (n = 26). †Values are means ± SD.

ECG = electrocardiogram; FDC = familial dilated cardiomyopathy; LVEDD = left ventricular end-diastolic dimension.

comprehensively reviewed (18), HCM has received extensive clinical and genetic investigation with medical, surgical and antiarrhythmic strategies for the treatment of affected individuals. Screening by history, exam and echocardiography of first-degree relatives of patients with HCM has been advocated for several years (19–21), with recent updated
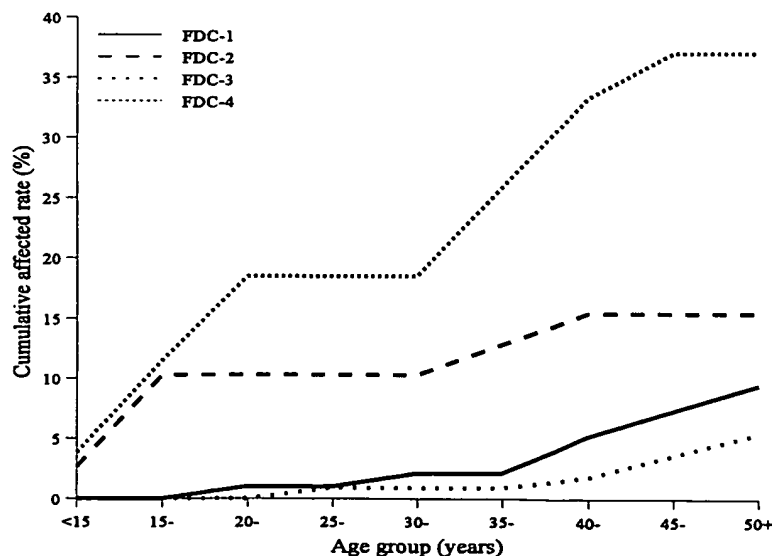
Figure 5. Cumulative rate of FDC by age group.

diagnostic criteria for adults in affected families (20). For HCM, it is recommended that any intervention be individualized, as the heterogeneity of HCM disease presentation and progression has limited the utility of generic treatment recommendations, especially for asymptomatic or mildly symptomatic patients (18–20). Screening for HCM and other cardiovascular genetic syndromes has also received additional attention in recent reviews outlining ethical mandates in genetic disease, with the foundational principles that screening activities must be voluntary from those potentially affected family members after full disclosure, and screening results must be combined with expert counseling for those found to be affected (21,22).

The situation with FDC is quite similar in some respects to that of HCM and in other respects fundamentally different. Similarities include the reality that affected family members in FDC (this work and others) or HCM (18,20) pedigrees are frequently asymptomatic. Also, both diseases can be life threatening from arrhythmias or heart failure, although the latter is more common with FDC. Differences include a twice-greater incidence and prevalence of IDC estimated at 6 per 100,000 person-years and 36.5 per 100,000, respectively (17). Perhaps the most fundamental difference is that FDC, as a subset of IDC, already has established clinical guidelines for the treatment of asymptomatic and symptomatic LVE based on extensive clinical investigation over the last 10 to 15 years (16), and these guidelines provide a foundation for generic recommendations regarding FDC.

For LVE in otherwise asymptomatic individuals, the use of ACE inhibitors demonstrated less progression to symptomatic heart failure in the Studies of Left Ventricular Dysfunction (SOLVD) prevention trial (23). For LVE in symptomatic patients, ACE inhibitors improved survival and quality of life (24–27). Even though the SOLVD and other trials with ACE inhibitors (24–27) were performed in patients with two fundamentally different etiologic causes of heart failure (ischemic and idiopathic dilated cardiomyopathies), the responses to therapy were similar with both etiologies. Based on the likelihood that from one-third to one-half of these patients assigned as IDC in these studies had FDC, these studies support the use of conventional medical treatment with ACE inhibitors for FDC to improve survival and prevent progression of disease. For FDC, this may be particularly relevant for screening of family members with asymptomatic LVE (23). The use of beta blockers in combination with ACE inhibitors may also be appropriate in these settings (28–30).

Clinical recommendations. Thus, the rationale for the clinical recommendations that follow are based on the serious, life-threatening nature of an IDC or FDC diagnosis, the ability to detect LVE easily and noninvasively by echocardiography with stringent, sensitive and reliable diagnostic echocardiographic criteria (13) and the knowledge that generic medical intervention with established treatment

protocols has a reasonable chance to affect the natural history of FDC. Based on these considerations, and assuming the voluntary participation of family members after comprehensive informed consent and the availability of counseling for all subjects as needed, we propose the following.

1. A search for an FDC diagnosis is appropriate when IDC is diagnosed.
   a. *Family history.* With a new diagnosis of IDC, a thorough cardiovascular family history should be obtained regarding first- and second-degree relatives who have known heart disease, heart failure or sudden death. If one first-degree or two second-degree relatives have been diagnosed with IDC, a diagnosis of FDC should be assigned.
   b. *Echocardiographic screening.* We suggest that echocardiographic screening for LVE is appropriate in first-degree relatives of patients diagnosed with IDC regardless of the cardiovascular family history. If LVE is discovered, a thorough medical evaluation should be undertaken to exclude other cardiovascular disease, and once excluded, a presumptive diagnosis of FDC should be assigned. The utility of screening of children (<16 years) is unclear due to the difficulty assigning LVE in this group and the age-dependent penetrance. If the family history and echo screening are negative, we advocate no further screening activities to establish the FDC diagnosis.
2. If the diagnosis of FDC is established in a kindred, we suggest that stepwise echo screening is indicated for first-degree relatives of those individuals diagnosed with FDC. We propose that first-degree relatives of those individuals diagnosed with FDC undergo echocardiographic screening for LVE. If additional affected subjects are identified, we propose that all first-degree relatives of those affected should undergo screening in a progressive stepwise format. For example, in the OHSU FDC-4 pedigree, after the assignment of the FDC diagnosis in the index patient (IV-8) based on IDC diagnoses in two second-degree relatives, we screened the index patient's father (III-9) (step 1) and found him to be affected by our diagnostic criteria, who in turn had eight siblings (his first-degree relatives). They underwent stepwise screening (step 2), and as shown, several additional family members were found to be affected (Fig. 4). By this recommendation, the first-degree relatives of those affected individuals from step 2 should likewise undergo screening (step 3). Thus, it is possible that progressive stepwise screening will identify affected individuals throughout an extended family.

   We suggest routine screening beyond first-degree relatives for clinical purposes is probably not indicated based on our present experience, although we note that by strict application of this guideline, the three affected children of subject III-14 in the FDC-4 pedigree would

not have been identified as he did not have LVE at the time of screening and thus was classified as unaffected. We propose two caveats to this recommendation: for an extended FDC family, we suggest that medical evaluations of members with unexplained cardiovascular symptoms is always appropriate; and if requested or for particularly aggressive disease, screening of second-degree relatives for LVE in some pedigrees may also be appropriate.

3. *Treatment intervention.* For all subjects diagnosed with FDC, we propose generic treatment with ACE inhibitors (and possibly beta blockers), as has been previously recommended for patients with IDC and asymptomatic LVE, or IDC and symptomatic heart failure (16).

4. *FDC counseling.* Family members diagnosed with FDC should be counseled that FDC has an unpredictable clinical course, which ranges from one that is relatively benign with conventional treatment to one of progressive heart failure, which may result in heart transplantation or sudden cardiac death. Additionally, affected family members should be informed that they have a heritable disease with a genetically transmissible risk to their offspring (50% probability with Mendelian dominant inheritance). Finally, those who are genetically at risk but have no evidence of LVE should be counseled about the age-dependent penetrance, the possibility of future disease presentation, and the recommendation for future surveillance screening, or screening at any time with symptoms of cardiac dysfunction.

5. *Surveillance screening.* Although firm recommendations are difficult, surveillance screening is probably indicated on a three- to five-year basis for first-degree relatives who at initial screening have been shown to be clinically unaffected.

Limitations. We recognize several limitations to the present work. First, although the clinical effectiveness of screening first-degree relatives of those with IDC to establish the diagnosis of FDC is apparent and is congruent with HCM recommendations, the cost effectiveness of FDC screening has not yet been validated. We suggest, however, that the potential benefit of early therapy for LV dysfunction to prevent symptomatic or progressive heart failure (23) in the subset of individuals found to have LVE will likely outweigh the costs of screening and drug treatment. The evaluation of comprehensive costs associated with screening of first-degree relatives will require a prospective design and is being initiated in our FDC research program at this time. Second, the lack of genotypic data for FDC limits predictive and prognostic information. Based upon multiple loci from the reports of FDC pedigrees from other groups (6–11) and the exclusion of these loci in the OHSU pedigrees presented here (Hershberger et al. (13), unpublished data), the molecular causes of FDC will be polygenic. Thus, it is possible that certain FDC genotypes will respond more or less favorably to these drug interventions. These shortcomings

may be more easily addressable for FDC as disease genes are identified, and as multiplexing gene technology emerges that will permit rapid and simultaneous screening of many genotypes, which will allow the creation of large databases to predict clinical outcomes based on genotypic data. Third, the echocardiographic screening for children (defined by our group as age <16 years) is problematic because of the lack of large, population-based standards for normal left ventricle size in children. Linear growth may be the major determinant of cardiac growth, and therefore of cardiac dimensions in children (31,32), but a host of factors influence normal childhood growth. A similar problem has been noted for screening of HCM in children (20).

Summary. In summary, we have demonstrated autosomal dominant patterns of inheritance in four large FDC pedigrees and that the age of onset of symptomatic clinical disease varies considerably among individuals. We have also demonstrated that family screening will reveal asymptomatic disease in first-degree relatives. This collective experience combined with extensive clinical research regarding the treatment of symptomatic and asymptomatic LVE and left ventricular dysfunction have led to preliminary recommendations for clinical practice relevant to FDC.

Acknowledgement

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